## IN THE SPECIFICATION

**Please revise the specification as follows.**

**Please replace in entirety paragraph 1 with the following:**

[0001] This application is a divisional of U.S. Patent application Ser. No. 09/692,857, filed Oct. 20, 2000. This application also claims priority to U.S. Provisional Patent Application Serial No. 60/161,130, filed Oct. 22, 1999 and to U.S. Provisional Patent Application No. 60/170,051, filed Dec. [~~9~~] **10**, 1999. All of these applications are incorporated herein by reference.

**Applicant brings to the attention of the Examiner that the date for this provisional application is correct on the Inventor's Declaration.**

**Please replace in entirety paragraph 34 with the following:**

[0034] Turning first to FIG. 1 there is shown a typical infusion apparatus 1000 commonly in use in most [~~modern~~] **modern** hospital settings. This apparatus administers infusate 1005 systemically to a patient 1007. Infusate fluid 1005 is contained in a plastic bag 1010, and the fluid is allowed to pass at some predetermined volumetric flow rate through plastic tubing and catheter setup 1015 and into an appropriate biological space, usually vascular. This space could be other body spaces or cavities capable of accepting positive volumetric flow, such as the peritoneum or cerebral spinal fluid space. This defines an "open" space or cavity as opposed to a closed or site specific location. Examples of other open spaces include the systemic circulation, [~~the cerebral spinal fluid space~~,] the lymphatic space, synovial fluid spaces and urinary fluid spaces.

**Please replace in entirety paragraph 37 with the following:**

[0037] The present invention relates to a system including a catheter assembly and a source of energy for releasing a compound into a biological space, such as the vascular system, peritoneum, cerebral spinal fluid space, or other biological spaces which can accept a volumetric flow rate of infusate. According to one embodiment of the present invention, a therapeutic agent such as a drug is linked by photolabile bonds to a polymer matrix surrounding a lumen of a catheter. Infusate fluid such as normal saline, 5% dextrose and water, lactated Ringer's solution, crystalloid solution, plasma or blood flows through the lumen of the catheter from a source of the infusate into the biological space. When it is desired to release the compound into the biological space, the polymer matrix surrounding the lumen and including the photolabily-linked compound is exposed to [~~the~~] energy such as light radiation. The radiation breaks the photolabile bonds, and the compound is released from the material such that it can diffuse into the infusate.

**Please replace in entirety paragraph 39 with the following:**

[0039] The present invention can provide an effective and efficient mechanism to exert an infusate concentration change for a compound delivery system with little or no volumetric changes. The clinical setting is an [~~immediate~~] example where compounds can be introduced by varying the concentration profile of a drug to alter the dose or mass of drug administered. This is a departure from the traditional manner of increasing the volume flow rate of intravenously administered drugs. The ease and rapidity of introducing new compounds to a given drug therapy provided by the present invention may be unmatched for some settings. In-line prodrug-drug interactions are possible. Developing drugs with previously prohibitive delivery characteristics, such as extremely short half-lives, may be delivered with this device.

**Please replace in entirety paragraph 49, with the following:** ***(includes removal of an extra space before the "." in front of the last sentence)***

[0049] A catheter assembly 20 according to one embodiment of the present invention has both drug storage and drug releasing properties, and the ability to transmit appropriate energy from a source of energy 35 into polymer matrix 55. A photo-activateable therapeutic agent delivery material is used, in which a therapeutic agent 65 is combined by covalent bonding, incorporation [~~20~~] in a matrix, or encapsulation, with a photosensitive macromolecule. In this combination, the drug is inert. The macromolecule is large enough to prevent migration of the combination within the catheter body, so that the combination can be in place during infusion or withdrawal of bodily fluids through the luminal space[ ]. A drug or other compound is released from the combination, in an active form, upon appropriate stimulation by the source of energy 35.

**Please replace in entirety paragraph 51 with the following:**

[0051] A wide choice of polymers 55 are available for this purpose. It is desirable that the polymer be biochemically acceptable and inert. It is further desirable that the polymer should possess chemical groups capable of reaction with a functional group of the photolabile compound such as the carboxylic acid group of BNBA or CPA, e.g. hydroxyl groups. It should also be capable of releasing the active drug freely, once the covalent chemical bonding has been broken. For example, the drug 65 should be able to diffuse out of the residual polymer matrix in the presence of infusate fluid. Examples of suitable polymers 55 include, but are not limited to polyvinyl alcohol (PVA), polyethylene oxide (polyethylene glycol PEG), acrylamide copolymers, vinylpyr[ɾ]olidone copolymers, hydroxyl functionalized polylactides, poly [-(-] hydroxyethyl methacrylate [-)-] (HEMA), copolymers of two or more such monomers, e.g. copolymers of vinylpyr[ɾ]olidone and HEMA, and copolymers of ethylene oxide and propylene oxide. The hydrogel polymer may also be selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyr[ɾ]olidone, maleicanhydride polymers, polyamides, polyvinyl alcohols, and polyethylene oxides or polyacrylic acid.

**Please replace in entirety paragraph 53 with the following:**

[0053] The hydrogel polymer matrix 55 deposition and affixation to the inner surface 52 of the catheter sheath 50 can be accomplished by the following example according to U.S. Pat. No. 5,304,121, incorporated herein by reference. The inner surface 52 of the catheter sheath 50 is coated with a solution of 4,4' diphenylmethane diisocyanate (MDI) in methylethylketone for 30 minutes. After drying in an air oven at 85 °C [∓] for 30 minutes, the sheath is dipped in a 1.7% solution of poly(acrylic acid) homopolymer having a molecular weight of about 3,000,000 in dimethylformamide (DMF) and tertiarybutyl alcohol. After drying at about 85 °C [∓] for 30 minutes, a smooth coating is obtained. The sheath is oven dried for 8 hours at 50 °C. One function of the drying steps is to remove solvent from the coating. The polyisocyanate solution is at a concentration of about 0.5 to 10% by weight. The polyacrylic acid is at a concentration of about 0.1 to 10% by weight. The poly(carboxylic acid) to polyisocyanate molar ratio is generally about 1:1. The formation of the hydrogel is well known in the art, such as the hydrogel further described in U.S. Pat. No. 5,091,205, incorporated herein by reference.

**Please replace in entirety paragraph 55 with the following:**

[0055] Energy for release of the drug in its active form from the drug-polymer combination can be by one of a variety of means depending upon the photosensitivities of the chosen photolabile bond, the polymer 50, and the drug 65. For example, the source 35 of energy can be radiation such as infrared, visible, or ultraviolet radiation, supplied from incandescent sources, natural sources, lasers including solid state lasers, or even sunlight. In one embodiment, the present invention contemplates the use of a source 35 of coherent light of wavelengths from about 300 nm to about 1200 nm. This includes UV, visible and infrared light. The choice of wavelength is based on the photolabile characteristics of the bonds holding 65 within 55 and is selected to match the wavelength necessary to break the photolabile bond between 65 and 55. Since body tissues tend to absorb radiation in the ultraviolet region of the electromagnetic spectrum, it is preferred to choose a photolabile bond sensitive to red and infrared wavelengths. The amount of drug released is proportional to the dosage of the radiation. Various agents for producing the [~~photoliable~~] **photolabile** bonds are described in related [ ~~are~~ ] **art** such as U.S. Patent No. 5,767,288, incorporated herein by reference.

**Please replace in entirety paragraph 61 with the following:**

[0061] The amount of storage volume is adequate to incorporate a substantial amount of drug to be used for various procedures. As best seen in FIG. 4, in one embodiment of the present invention the inner wall 52 of sheath 50 has a diameter $D_2$ of about 3.6 mm, and the lumen formed by polymer matrix 55 has a diameter $D_1$ of about 2.6 mm. The total length $L_1$ of the portion of the catheter 20 incorporating the polymer matrix is 1.7 meters. The cross-sectional area $A_1$ is calculated as $\pi(D_2^2-D_1^2)/4$ and is 4.84 $mm^2$. The total volume $V_1$ of the polymer matrix is 8.23 $cm^3$. This is a representative volume calculation and provides an estimate of a catheter body matrix 55 volume that would be available for drug incorporation for the present invention. There is no general restriction of the tubing diameter of the portion of the present invention that resides outside the vasculature. It is anticipated that an 8-12 $cm^3$ volume of catheter matrix material 55 would be sufficient to incorporate substantial amounts of drug(s) into the polymer matrix for delivery into the infusate and further into the systemic circulation or receiver space. Much larger reservoirs for drug storage can be realized for portions of the present [~~designed~~] **design** to be extravascular in nature. By controlling the concentration of the therapeutic agent 65 within matrix 55, the total amount of therapeutic agent 65 available for infusion can be limited by control of the thickness and length of the polymer matrix. For example, the total amount of therapeutic agent stored in a particular catheter assembly 20 can be limited to an amount that is safe for delivery under any conditions. Jacketed conditioning of the tubing extravascularly, such as for temperature or radiation exposure, can also be provided for extravascular portions of the present invention to allow for better inline processing of fluids or for maintaining the integrity of the catheter body matrix or compounds stored therein.

**Please replace in entirety paragraph 65 with the following:** ***(includes inserting a period after the word "modalities")***

[0065] The catheter or tubing 20 would release compound into contents of body fluid, such as, blood, cerebral spinal fluid, cardiac pericardial fluid, lymph, during outflow, adding pretreatment compounds, such as anticoagulant, antibiotic, anti-thrombotic or other conditioning or treatment agents proximal to entrance into the dialysis or other equipment. Upon exit from a treatment apparatus, such as dialysis or chemotherapy devices, and prior to return into the living system, further conditioning compounds could be released into the luminal tubing space to deactivate or activate functionalities in the treated body fluids. The advantage of maintaining sterile or otherwise separate conditions during such extra-corporal closed loop treatments is realized. It is anticipated that the tubing designed from the present invention could be incorporated into the interior of an apparatus for dialysis or other inline treatment regimen, such as during lymphatic or [ ~~lucemic~~ ] **leukemic** cancer treatment or other disease amenable to fluid treatment modalities**.** The permanent withdrawal of fluids for diagnostic sample collection can be pretreated during collection with another embodiment of the present invention. As seen in FIG. 11, system 400 withdraws bodily fluid from a biological unit and conditions that fluid for subsequent use during testing or analysis of the fluid. Fluid is withdrawn from a biological unit 30 through a catheter 20 which is in fluid communication with a fluid receiver 410, receiver 410 including a suction pump or other means for withdrawing fluid. As the fluid passes through catheter 20, energy source 35 provides energy through conduit 40 into the polymer matrix of catheter 20, such that a compound releasably captured in the polymer matrix is released into the bodily fluid flowing into receiver 410. For example, the bodily fluid can be blood, and the compound released from the polymer matrix can be an anticoagulant. Addition of anticoagulant, antibodies, or dyes prior to sample

preparation can aid in the accuracy, reliability and speed of such clinical testing. This sample conditioning could extend to any sample fluid obtained through such tubing, including lymph, CSF, certain biopsy material and urine. It is also anticipated that various laboratory, experimental, industrial or non-biological processes or settings can incorporate the present invention and method thereof for the purposes of adding compounds to an inline process.

**Please replace in entirety paragraph 68 with the following:**

[0068] The section of tubing 520 containing the releasably captured compound and the matrix material is the same as catheter assembly 20, except as shown and described differently. The sheath material for tubing 520 does not need to be either biocompatible nor flexible and may be constructed from any material which transmits the energy into the matrix material. The compound releasably captured within the matrix of tubing assembly 520 does not need to be biocompatible or provide therapeutic affect, and may be any material which can be releasably captured within the matrix material and subsequently released by the application of energy to the matrix material. Energy source 535 is the same as energy source 35, except as shown and [~~describe~~] **described** differently. Energy source 535 does not need to be biocompatible in terms of the quantity or quality of energy released.

**Please replace in entirety paragraph 69 with the following:**

[0069] Another embodiment of the present invention relates to a method for manufacturing a catheter assembly. The catheter includes one end that is readily attachable to a laser or non-laser light source. FIGS. 8 and 9 depict a molded outer sheath 50' of laser light conductible fiber optic material and incorporating multiple baffles 253 and 254 to center an inner rod 252 used during assembly of the catheter. Baffles 253 and 254 are semicircular in shape and are integrally molded into sheathing 50'. Each baffle preferably includes a semicircular [~~cut-out~~] **cutout** 257 and 258, respectively. These [~~cut-outs~~] **cutouts** are shaped to accept and support a form coated with polymer matrix, such as rod 252 coated with hydrogel 55.

**Please replace in entirety paragraph 72 with the following:** ***(includes inserting a period after the word "art" at the end of the paragraph)***

[0070] The light carrying section of the outer fiber optic sheath 50 and 50' can be of any thickness that conducts the proper intensity of light. The preferred fiber optic sheath will have a cross sectional area from about 200 to about 3000 microns and preferably about 1200 microns. The choice of the sheath cross sectional area depends on the brightness of the light source and the optical power output required for release of the drug from polymer matrix. In some embodiments, the sheath provides the structural integrity and flexible characteristics of the overall catheter tubing. This material is readily available to one of ordinary skill in the art.

**Please replace in entirety paragraph 71 with the following:**

[0071] As shown in FIGS. 8 and 9, the catheter sheath 50' is a split cylinder, with the split occurring lengthwise along the sheath. The sheath includes only a single split 251, such that the sheath 50' preferably remains one piece. In some embodiments of the present invention, the molded sheath includes a hinge section 280, such as [~~and~~] **an** area of weakened material, on the side of the sheath opposite the split. This hinged area 280 facilitates a bending apart of the two lengthwise sections of the molded sheath 50'. The two sections can be hinged away from one another so as to facilitate the later insertion of a rod 252 in the central [~~cut-out~~] **cutout** of the baffles.

**Please replace in entirety paragraph 72 with the following:**

[0072] A biocompatible hydrogel polymer matrix 55 which includes the photolabily bonded therapeutic agent 65 is deposited upon a rod 252 designed to loosely bind the gel material. The rod is composed of a material such as a hard plastic. The surface does not bind tightly to the gel, which may be **a** property of the hard plastic itself or a property of a rod coating substance such as TEFLON® provided to coat the surface of the rod. The polymer 55 thickness is allowed to build up in the hydrated state around the rod 252 to a thickness such that the volume of the matrix 55 and rod 252 together become greater than the internal volume of the closed catheter sheathing. Various sections of hydrogel material may be included such that each section might incorporate unique compounds or groups of compounds distinct from other sections with regard to their confinement properties and releasing characteristics.

**Please replace in entirety paragraph 73 with the following:**

[0073] The sheath is formed around the rod-hydrogel section, as seen in FIG. 9. The bent-apart sheath sections are brought back into contact, which may result in a partial squeezing out of some of the hydrogel [~~in~~] **and** therapeutic agent. The lengthwise split 251 is sealed by a method such as adhesion with a bonding agent or ultrasonic welding. The inner surface 52' of the sheath 50', including the baffles 253 and 254, are preferably prepared to accept the hydrogel via adhesive preparation according to U.S. Patent No. 5,304,121 and designed to accept the hydrogel 55 and affix it to the catheter sheath interior prior to assembly with the rod-gel section.

**Please replace in entirety paragraph 74 with the following:**

[0074] The assembly is allowed to dry, the subsequent dehydration causing the thickness of the hydrogel to decrease by as much as a factor of 6-10. This substantial reduction in volume permits the hydrogel to pull away from the surface of rod 252, since the adhesion of the hydrogel to the rod surface is less than the adhesion of the hydrogel to the inner surface 52' of the sheathing 50'. The rod 252 is then removed, and the sheath is coated on the outer surface with an opaque and reflective coating combination 70 and 75. These coatings can also incorporate a sealer to provide a means to close the seam 251 remaining after the sheath circumscribes the rod-hydrogel section, or a separate step may be needed to close the seam prior to coating. When rehydrated during use the polymer matrix 55 swells and reforms to a shape that allows a lumen 60 to form with a diameter generally determined by the central [~~cut-outs~~] **cutouts** of the baffle and the outer diameter of the rod. Appropriate sterile procedures are followed for tubing that is manufactured for parenteral use, such that either suitable sterilization techniques compatible with the catheter materials are followed for components prior to assembly or appropriate post-manufacturing sterilization procedures are carried out, such as radiation bombardment.

**In addition to the change to the word "cutouts" shown below, Applicant brings to the attention of the Examiner that the published version of this paragraph erroneously uses boldfacing in the second sentence as follows:**

currently published as: As best seen in FIG. 8, **a** portion . . .
should be: As best seen in FIG. 8, a portion . . .

**Please replace in entirety paragraph 75 with the following, and including the boldfacing changes shown above:** ***(includes inserting a period after the word "energy" at the end of the paragraph)***

[0075] Another embodiment of the present invention contemplates a catheter assembly incorporating two different therapeutic agents 65 and 66 which are not mixed within the polymer matrix, and are separated into different sections of the catheter. As best seen in FIG. 8, a portion 55a of the polymer matrix including captured therapeutic agent 65 coats a first portion of rod 252. A portion 55b of the polymer matrix including captured therapeutic agent 66 coats a second portion of rod 252. As coated road 252 is placed within the baffle [ ~~cut-outs~~ ] **cutouts**, therapeutic agent 65 is largely confined to section 259a of sheath 50', defined between baffles 254a and 254b, and between baffles 253a and 253b. Therapeutic agent 66 is largely confined to section 259b of sheath 50', defined between baffles 254b and 254c, and between baffles 253b and 253c. An arbitrary number and placement of such said sections can be incorporated into the sheath of the present invention. Further, these sheath sections can be supplied by separate laser light pipes capable of transmitting multiple distinct wavelengths of laser energy**.**

**Please replace in entirety paragraph 76 with the following:**

[0076] According to another embodiment of the present invention, catheter 20 is manufactured using a split, bent-apart, molded sheath 50'[,] . Sections of a polymer matrix such as 55a and/or 55b are placed within the interior sections 259a or 259b of sheath 50'. A rod 252 which is preferably not coated with a polymer matrix is placed within sheath 50', preferably being supported within the cutouts 257 or 258 of the baffles. The interior surface 52' of sheath 50' is preferably coated as previously described to improve the adhesion of the polymer matrix to surface 52'. Sheath 50' is then formed around rod 252, with split 251 being adhered closed as previously described. The polymer matrix is then shrunk in volume, such as by dehydrating. Rod 252 is removed from the closed sheath. Sheath 50' can include a first section 259a containing a first releaseably captured compound 65, and a second section 259b containing a second releaseably captured compound 66.

**Please replace in entirety paragraph 82 with the following:** ***(includes removal of an extra space on the third line before the ".")***

[0082] The advantages of this device are increased safety to the recipient of infused drug through decreased trauma of infusion site innervations and for maximum maintenance of sterile conditions[ ]. Catheters can be used for either short-term or long-term vascular access. Factors associated with infusion-related phlebitis among patients with peripheral venous catheters [~~including~~] **include** site of catheter insertion, experience of personnel inserting the catheter, frequency of dressing change, catheter-related infection, skin preparation, host factors, and emergency-room insertion could all be decreased from use of the present invention. The present invention provides increased safety for general catheter use by providing a drug or other compound to be made immediately available for use when needed for adjunctive therapy without adding any extra equipment into the sterile infusion set environment. This is in contrast to the necessity with current practices for an additional catheter to be inserted, a drug solution to be changed, or any of various other alterations necessary to add adjunctive drug therapy using **a** catheter or tubing system. The present invention provides [~~quicker~~] **quick** and accurate drug delivery of on-demand doses of new or concurrent multi-drug therapies. The present device can be programmed to release drug at a specified time and in a controlled amount with a degree of accuracy based upon the high degree of accuracy available through computer control of an energy source. The computer control allows administration of a specified and appropriate amount of intensity and duration of energy exposure, preferably coherent light, to the catheter sheath for subsequent release of agents 65 and 66 into infusate solution.

**Please replace in entirety paragraph 83 with the following:**

[0083] The drug is also released into the catheter lumen which may extend up to and sometimes inside the vasculature setting. A more immediate entrance into a positive flow body cavity space, such as the systemic circulation can be realized with the present device, where drug is stored and released at the opening of a catheter inside the vasculature. This is in contrast to a current adjunctive processes including providing drug into a port which has to travel down the catheter tubing and then enter the systemic circulation. In such cases an attendant is necessary to mix a drug and inject it into the infusion set port, which takes time and adds an element of human error to the process. In some situations a common syringe pump apparatus **is** in place to administer the adjunctive drug therapy. The present invention has few mechanical parts to fail. The infusion pump apparatus involves many moving parts which increases the risk of malfunction. Both attendant and syringe pump apparatus therapy modifiers inject an added volumetric input to the flow of infusate, thereby limiting their effectiveness if the total flow rate into the biological unit must be limited to a maximum amount. Both adjunctive processes also use a constant concentration of added infusate, so that dynamic changes in dose require dynamic changes in injected infusate volume.

**Please replace in entirety paragraph 84 with the following:**

[0084] Some embodiments of the present invention incorporate a therapeutic agent 65 with a short half-life into the polymer matrix 55. Because of the short time lag from release of the drug from the matrix into the vasculature of the patient, there is increased effectiveness of the short[ -] half-life agent. Examples of these type of drugs would include short acting anesthetic agents such as xylocaine and cardiac agents such as nitrous oxide derivatives, and prostaglandin derivatives. An operator may afford effective feedback control of short acting cardiac drugs, analeptics, neurotransmitters, analgesics, or hormones. During the monitoring of an EKG of a patient in the intensive care unit of a hospital, when arrhythmias are detected or cardiac arrest is indicated, a drug can immediately be released into the systemic circulation for therapy. While monitoring the EEG during anesthesia, drugs can be released into the systemic circulation by the present invention to decrease or increase the depth of anesthesia through proper release of drugs.

**Please replace in entirety paragraph 85 with the following:**

[0085] The present invention can be used to administer drug in an automatic, easily controlled manner. Traditional drug regimens have included administering drugs orally, sublingually, rectally, subcutaneously, intramuscularly, occularly and parenterally. The regimens with respect to time have included rapid injections, constant rate infusions and combinations thereof. The present invention can be used to administer drug or compound when that drug or compound is administered by a tubing or a catheter system. To deliver any arbitrarily administered drug regimen, a computer controller is programmed **to** control energy source 35 to administer a defined energy magnitude or duration to the tubing matrix of the present invention so that a proportional amount of stored compound is released into the tubing lumen in a controlled manner. The ease of input profile generation used to control drug release from the present inventions, coupled with their potentially complex characteristics with respect to time represent a very flexible means of drug delivery when traditional methods of drug delivery are considered. A patient can in many instances self-administer the radiation to release drug on an "as required" arbitrary basis, e.g. for hypertension treatment or for pain relief.

**Please replace in entirety paragraph 87 with the following:**

[0087] Unpredictable changes over time t of a quantity V is known as noise V(t). The spectral density of V(t), $S_V(f)$, gives an estimate of the mean square fluctuations of the quantity at a frequency f. As seen in FIG 13A, by plotting log $S_V(f)$ as a function of log f, a slope can be calculated, and this slope can be interpreted as having a functional form $1/f^{\beta}$ [÷] , where $\beta$ is a spectral exponent. Plot 605 of FIG. 13A plots the spectral density of a variable where $\beta$ **is** equal to 1. Graph 610 represents the log of the spectral density of a variable for $\beta$ equal to 2. A particular finding has included the discovery that almost all musical melodies mimic 1/f noise, where 1 is equivalent to "white" noise, and $1/f^2$ corresponds to Brownian motion.

**Please replace in entirety paragraph 88 with the following:**

[0088] Fractional Brownian motion (fBm) is a mathematical model for many random fractals found in nature, including 1/f noise. Formally, it is the increments of fBm (the differences between successive values) that produce values corresponding to various $1/f^{\beta}$ noise series. Traces of fBm are characterized by a parameter H in the range of $0 < H < 1$. The value $H \approx 0.8$ is empirically a good choice for many natural phenomena. [~~Fractal~~] **Fractional** Brownian motion has been studied and various methods of generating trains of 1-, 2- and 3-dimensional data sets have been developed; see: The Science of Fractal Images, Eds. Heinz-Otto Petigen and Dietmar Saupe, 1988. These include spatial approximation methods and [~~,~~] approximation by spectral synthesis. These methods can readily be carried out by ordinary computer analysis. According to another embodiment of the present invention, the application of energy to the catheter assembly is applied according to a 1-dimensional algorithm to synthesize fBm [~~fractal Brownian motion~~] (**fractional Brownian motion**).

**Please replace in entirety paragraph 89 with the following:**

[0089] FIG. 7 schematically depicts a system 150 for delivering therapeutic agent in a fractally-based pulsatile manner to a biological unit 30. An electronic controller 155 produces a fractally derived signal 157 to control an energy source 35', such as a laser. Various methods of generating fBm numerical time series can be used to calculate fractally-based signal 157 by controller 155, such as with [~~fast~~] **Fast** Fourier Transform filtering, random midpoint displacement methods, or other methods described in The Science of Fractal Images, Eds. Heinz-Otto Petigen and Dietmar Saupe, 1988. FIG. 13B-D represent three distinct fBm curves [~~Vi(t)~~] $V_i(t)$ synthesized using the midpoint displacement method to produce fBm, where H=0.8. The fractally derived control signal 157 can also be generated by choosing a value of β, preferably between the values of 0.5 and 1.5. From selection of either H or β, the log of the spectral density of a pulse parameter such as magnitude, duration, and separation interval can be predicted. FIG. 13B, 13C, and 13D represent three distinct fBm curves 620, 630, and 640, respectively, for [~~Vi(t)~~] $V_i(t)$ synthesized using the midpoint displacement method for a selected value of H. Curve 620 of FIG. 13B represents a fractally derived series of laser pulse magnitudes at 6 intervals. FIG. 13C represents a series of fractally derived laser pulse durations at 6 intervals. FIG. 13D represents a series of 6 fractally derived laser pulse spacing intervals. These series have been sampled at regular intervals, [~~Si,~~] $S_i$, to determine the value of the quantity at the particular sampling time. These [ ~~value~~ ] **values** are used to assign values to laser pulse parameters. Each pulse is characterized by the parameters of pulse magnitude, ($V_1$), duration, ($V_2$), and separation interval, ($V_3$), from the immediately preceding pulse in the series, [~~Sp(i)~~] $S_p(i)$.

**In addition to the changes shown below, Applicant brings to the attention of the Examiner that the published version of this paragraph should use boldfacing in the second and third sentences as follows:**

currently published as: A time domain pulse train is shown in FIG. 13E, and is synthesized by combining the pulse series of FIG. 13**B**, 13**C**, and 13D. As shown in FIG. 13E, . . .

should be: A time domain pulse train is shown in FIG. 13**E**, and is synthesized by combining the pulse series of FIG. 13**B**, 13**C**, and 13**D**. As shown in FIG. 13**E**, . . .

**Please replace in entirety paragraph 90 with the following, and including the boldfacing changes shown above:**

[0090] Numerically, each of these values conforms independently to a fractally-based algorithm for each pulse to produce a fractally derived, time domain pulse train signal, **$S_p(i)$,** at the series sampling times as shown in FIG. 13E. A time domain pulse train is shown in FIG. 13E, and is synthesized by combining the pulse series of FIG. 13B, 13C, and 13D. As shown in FIG. 13E, there is a first pulse 645 with a magnitude of 5, duration of 5, and an interval spacing of 5 from the origin. A second pulse 650 from sampling interval 2 has a magnitude of 6, a duration of 2, and is spaced 6 units from pulse 645. Pulse 655 has a magnitude of 3, a duration of 3, and is spaced 9 units from pulse 650. The pulse train represented in FIG. 13E represents a model for the laser control signal 157. The pulse train of FIG. 13E is scaled by the appropriate intensity and time factors to take into account the specific embodiment of the invention, considering factors such as the effect of the chosen releasable compound, the volumetric flow rate of the infusate, the rate at which the particular laser breaks the particular [~~phtolabile~~] **photolabile** bonds, and other factors. For example, with certain specific therapeutic agents, the time interval shown could be minutes, where as for other specific therapeutic agents the time interval could be hours. As an alternate to the method described above, the present invention contemplates using

the difference between successive magnitudes [~~are used~~] to assign values to pulse parameters. For example of this alternate embodiment, the difference between successive values of FIGS. 13B, 13C, and 13D would be used to generate the time domain pulse train, instead of the values themselves.